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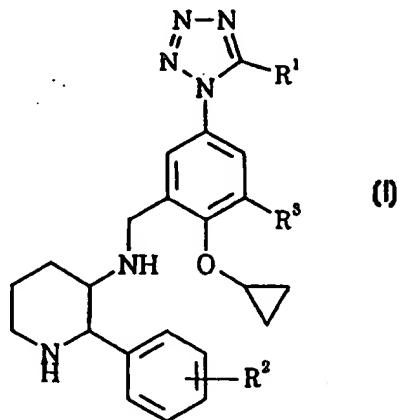
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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## (54) Title: PIPERIDINE DERIVATIVES AND THEIR USE AS TACHYKININ ANTAGONISTS



## (57) Abstract

Substituted piperidine derivatives of structural formula (I), wherein R<sup>1</sup> represents a hydrogen atom or a methyl or trifluoromethyl group; R<sup>2</sup> represents a hydrogen or halogen atom; and R<sup>3</sup> represents a hydrogen or halogen atom; and pharmaceutically acceptable salts thereof are tachykinin receptor antagonists of use, for example, in the treatment or prevention of pain, inflammation, migraine, emesis, postherpetic neuralgia, depression and anxiety.

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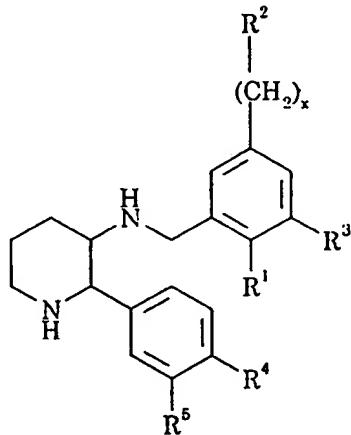
## PIPERIDINE DERIVATIVES AND THEIR USE AS TACHYKININ ANTAGONISTS

This invention relates to piperidine derivatives and their use as  
 5 tachykinin antagonists, and in particular as neurokinin-1 receptor  
 antagonists.

We have now found a class of piperidine derivatives which are  
 potent receptor antagonists of tachykinins, especially of the neurokinin-1  
 (substance P) receptor. In addition, the compounds of the present  
 10 invention exhibit a high level of hepatic stability as measured by, for  
 example, conventional liver microsome analysis.

International Patent Specification Nos. WO 95/08549 and WO  
 96/29326 disclose NK-1 receptor antagonists of the general structural  
 formula (A)

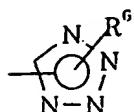
15



(A)

wherein

R<sup>1</sup> is a C<sub>1-4</sub>alkoxy group;  
 20 R<sup>2</sup> is



R<sup>3</sup> is a hydrogen or halogen atom;

R<sup>4</sup> and R<sup>5</sup> may each independently represent a hydrogen or halogen atom, or a C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy or trifluoromethyl group;

R<sup>6</sup> is a halogen atom, or a C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>m</sub>cyclopropyl, -S(O)<sub>n</sub>C<sub>1-4</sub>alkyl,

5 phenyl, NR<sup>7</sup>R<sup>8</sup>, CH<sub>2</sub>C(O)CF<sub>3</sub> or trifluoromethyl group;

R<sup>7</sup> and R<sup>8</sup> may each independently represent a halogen atom, or a C<sub>1-4</sub>alkyl or acyl group;

x is zero or 1;

n is zero, 1 or 2; and

10 m is zero or 1.

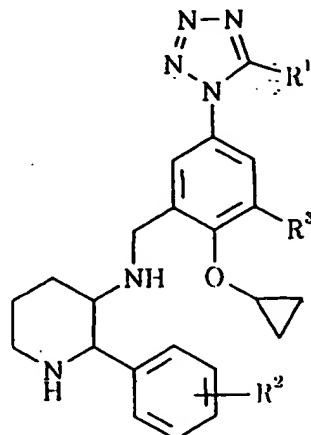
International Patent Specification No. WO 96/21661 discloses NK-1 receptor antagonists of the structural formula (A) wherein R<sup>2</sup>-R<sup>8</sup>, x, n and m are essentially as previously defined, and R<sup>1</sup> is -O-(CH<sub>2</sub>)<sub>p</sub>C<sub>3-7</sub>cycloalkyl (wherein p is zero or 1), -O-C<sub>1-7</sub>fluoroalkyl, or -O-(CH<sub>2</sub>)<sub>n</sub>X (wherein n is 1 or 2); where X is selected from C(O)NR<sup>7</sup>R<sup>8</sup>, C(O)R<sup>9</sup>, NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, 15 NHSO<sub>2</sub>R<sup>9</sup>, S(O)<sub>n</sub>R<sup>9</sup>, OC<sub>1-4</sub>alkyl, NO<sub>2</sub>, CO<sub>2</sub>H, CO<sub>2</sub>C<sub>1-4</sub>alkyl, CN or, when n is 2, X may also represent OH, SH or NH<sub>2</sub>.

WO 96/21661 defines an -O-(CH<sub>2</sub>)<sub>p</sub>C<sub>3-7</sub>cycloalkyl group as being, for example, cyclopropyloxy, cyclopropylmethoxy, cyclobutyloxy, cyclobutylmethoxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy. A 20 preferred class of compound in WO 96/21661 is defined as compounds wherein the group R<sup>1</sup> is a cyclopropylmethoxy, cyclopentyloxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy or, more preferably, a fluoromethoxy group.

25 From within the general class of compound disclosed by the aforementioned patent specifications, we have now identified a novel subclass of compound which, by virtue of their unique cyclopropyl ether moiety, possess a high degree of oral bioavailability together with a high affinity for the human NK-1 receptor. A further advantage of the 30 compounds of the present invention is their enhanced duration of action.

Preferably, the compounds of the present invention possess both a high degree of oral bioavailability and an enhanced duration of action.

The present invention accordingly provides the compounds of the formula (I):



(I)

5

wherein

R<sup>1</sup> represents a hydrogen atom or a methyl or trifluoromethyl group;

R<sup>2</sup> represents a hydrogen or halogen atom; and

R<sup>3</sup> represents a hydrogen or halogen atom;

10 or a pharmaceutically acceptable salt thereof.

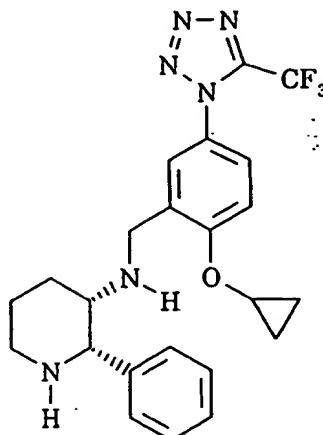
Particularly preferred compounds of formula (I) are those wherein

R<sup>1</sup> represents a hydrogen atom or a trifluoromethyl group. Most especially, R<sup>1</sup> represents a trifluoromethyl group.

15 Further preferred compounds of formula (I) are those wherein R<sup>2</sup> represents a hydrogen, fluorine or chlorine atom. Especially preferred are those compounds of formula (I) wherein R<sup>2</sup> is a hydrogen atom or a 4-fluorine atom. Most especially, R<sup>2</sup> is a hydrogen atom or a 4-fluorine atom.

20 Also preferred are compounds of formula (I) wherein R<sup>3</sup> represents a hydrogen, fluorine or chlorine atom. Especially preferred are those compounds wherein R<sup>3</sup> is a hydrogen or fluorine atom, in particular, a hydrogen atom.

A particularly preferred compound of the present invention is the compound of formula (Ia)



(Ia)

5

or a salt thereof, especially a pharmaceutically acceptable acid addition salt thereof. Most aptly the compounds of the formula (I) and (Ia) are the (2S,3S) stereoisomer.

Specific compounds of the present invention include:

10 N-{{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-phenylpiperidin-3-amine;  
 (2S,3S)-N-{{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-phenylpiperidin-3-amine;  
 N-{{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-(4-fluorophenyl)piperidin-3-amine;  
 15 or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention, the compounds of formula (I) may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

20 For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable

pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, 5 tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

10 The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a 15 suitable ion exchange resin.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

20 The compounds according to the invention have at least two asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. The 2S,3S stereoisomer is particularly preferred.

25 The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

30 Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, wafers, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers, are particularly preferred.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as

tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, LipoSyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents,

or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably 5 sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally 10 or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into 15 association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular 20 substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and 25 cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety 30 disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders,

brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, 5 vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced 10 parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and 15 aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delerium, withdrawal delerium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; 20 epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic 25 cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and 30 conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid

arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, bronchospasm and cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrosis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including

inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intracranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy,

vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents, including those routinely used in cancer chemotherapy, and emesis induced by other pharmacological agents, for example, rolipram.

5 Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, 10 vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

15 Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin 20 (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

25 The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

30 It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of

emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT<sub>3</sub> antagonist, such as 5 ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide or domperidone or GABA<sub>B</sub> receptor agonists such as baclofen. Additionally, a compound of formula (I), either alone or in combination with one or more other anti-emetic therapeutic agents, may be 10 administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone, betamethasone, triamcinolone, triamcinolone acetonide, flunisolide, budesonide, or others such as those disclosed in US patent nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712. Dexamethasone (Decadron<sup>TM</sup>) is 15 particularly preferred. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

20 When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. Pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the 25 treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, 30 temporomandibular pain, and maxillary sinus pain.

The compounds of formula (I) are also particularly useful in the treatment of depression including depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression 5 including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias; seasonal affective disorder; or depression.

10 The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

15 The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a 20 compound of formula (I).

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a compound according to the present invention and one or more other pharmacologically active agents suitable for the treatment of the specific 25 condition. The compound of formula (I) and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination.

Thus, for example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a 30 bronchodilator, such as a  $\beta_2$ -adrenergic receptor agonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and

the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D<sub>4</sub> antagonist such 5 as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

10 The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

15 The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

20 It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT<sub>1</sub> agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

25 For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent such as a bradykinin receptor antagonist.

30 The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agent include norepinephrine 5 reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists,  $\alpha$ -adrenoreceptor antagonists and atypical anti-depressants.

10 Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: 15 amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Suitable selective serotonin reuptake inhibitors include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

20 Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof.

25 Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, 30 WO 94/13661, WO 94/13676 and WO 94/13677.

Suitable atypical anti-depressants include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof.

5 Suitable classes of anti-anxiety agent include benzodiazepines and 5-HT<sub>1A</sub> agonists or antagonists, especially 5-HT<sub>1A</sub> partial agonists, and corticotropin releasing factor (CRF) antagonists.

Suitable benzodiazepines include: alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.

10 Suitable 5-HT<sub>1A</sub> receptor agonists or antagonists include, in particular, the 5-HT<sub>1A</sub> receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

15 Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an anti-depressant or anti-anxiety agent, together with at least one pharmaceutically acceptable carrier or excipient.

20 In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an anti-depressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety.

25 It will be appreciated that for the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders, a compound of the present invention may be used in conjunction with other anorectic agents.

The present invention accordingly provides the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for the treatment or prevention of eating disorders.

30 The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an amount of a compound of formula

(I) and an amount of an anorectic agent, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) and an 5 anorectic agent, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the compound of formula (I) and anorectic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention 10 of eating disorders. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a compound of formula (I) and an anorectic agent as a combined preparation for simultaneous, separate or 15 sequential use in the treatment or prevention of eating disorders.

In a further embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for the treatment or prevention of obesity.

The present invention also provides a method for the treatment or 20 prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an anorectic agent, such that together they give effective relief.

In an alternative embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for 25 the manufacture of a medicament for the treatment or prevention of bulimia nervosa.

The present invention also provides a method for the treatment or prevention of bulimia nervosa, which method comprises administration to a patient in need of such treatment an amount of a compound of formula 30 (I) and an amount of an anorectic agent, such that together they give effective relief.

In a further embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for the treatment or prevention of compulsive eating disorders.

5 The present invention also provides a method for the treatment or prevention of compulsive eating disorders, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an anorectic agent, such that together they give effective relief.

10 In an alternative embodiment of the present invention there is provided the use of a compound of formula (I) and an anorectic agent for the manufacture of a medicament for reducing the total body fat mass in an obese mammal, especially a human.

15 The present invention also provides a method for reducing the total body fat mass in an obese mammal, especially a human, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an anorectic agent, such that together they give effective relief.

20 Suitable anorectic agents of use in combination with a compound of the present invention include, but are not limited to, aminorex, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cycledredine, dexfenfluramine, dextroamphetamine, diethylpropion, diphenmethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, 25 fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

30 Particularly preferred anorectic agents include amphetamine and derivatives thereof such as amphetamine, benzphetamine,

chlorphentermine, clobenzorex, cloforex, clotermine, dexfenfluramine, dextroamphetamine, diethylpropion, *N*-ethylamphetamine, fenfluramine, fenproporex, furfurylmethylamphetamine, levamfetamine, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, 5 phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

A particularly suitable class of anorectic agent are the halogenated amphetamine derivatives, including chlorphentermine, cloforex, clotermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; 10 and pharmaceutically acceptable salts thereof.

Particularly preferred halogenated amphetamine derivatives of use in combination with a compound of the present invention include: fenfluramine and dexfenfluramine, and pharmaceutically acceptable salts thereof.

15 It will be appreciated that for the treatment or prevention of obesity, the compounds of the present invention may also be used in combination with a selective serotonin reuptake inhibitor (SSRI).

The present invention accordingly provides the use of a compound of formula (I) and an SSRI for the manufacture of a medicament for the 20 treatment or prevention of obesity.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of formula (I) and an amount of an SSRI, such that together they give effective relief.

25 In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of obesity comprising a compound of formula (I) and an SSRI, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the compound of formula (I) and SSRI 30 may be present as a combined preparation for simultaneous, separate or

sequential use for the treatment or prevention of obesity. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a compound of formula (I) and an SSRI as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of obesity.

In an alternative embodiment of the present invention, there is provided the use of a compound of formula (I) and an SSRI for the manufacture of a medicament for reducing the total body fat mass in an obese mammal, especially a human.

The present invention also provides a method for reducing the total body fat mass in an obese mammal, especially a human, which method comprises administration to the mammal an amount of a compound of formula (I) and an amount of an SSRI, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition for reducing the total body fat mass in an obese mammal, especially a human, comprising a compound of formula (I) and an SSRI, together with at least one pharmaceutically acceptable carrier or excipient.

Suitable selective serotonin reuptake inhibitors of use in combination with a compound of the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

As used herein "obesity" refers to a condition whereby a mammal has a Body Mass Index (BMI), which is calculated as weight per height squared ( $\text{kg}/\text{m}^2$ ), of at least 25.9. Conventionally, those persons with normal weight, have a BMI of 19.9 to less than 25.9.

The obesity herein may be due to any cause, whether genetic or environmental. Examples of disorders that may result in obesity or be the cause of obesity include overeating and bulimia, polycystic ovarian

disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, Type II diabetes, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g., children with acute lymphoblastic leukemia.

5 "Treatment" (of obesity) refers to reducing the BMI of the mammal to less than about 25.9, and maintaining that weight for at least 6 months. The treatment suitably results in a reduction in food or calorie intake by 10 the mammal.

15 "Prevention" (of obesity) refers to preventing obesity from occurring if the treatment is administered prior to the onset of the obese condition. Moreover, if treatment is commenced in already obese subjects, such treatment is expected to prevent, or to prevent the progression of, the medical sequelae of obesity, such as, e.g., arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

20 Thus, in one aspect, this invention relates to the inhibition and/or complete suppression of lipogenesis in obese mammals, i.e., the excessive accumulation of lipids in fat cells, which is one of the major features of human and animal obesity, as well as loss of total body weight. In another aspect, the invention ameliorates the conditions that are a consequence of the disease, such as preventing or arresting the progression of polycystic ovarian disease so that the patient is no longer infertile, and increasing the insulin sensitivity and/or decreasing or eliminating the need or usage 25 of insulin in a diabetic patient, e.g., one with adult-onset diabetes or Type II diabetes.

30 A further aspect of the present invention comprises the use of a compound of formula (I) for achieving a chronobiologic (circadian rhythm phase-shifting) effect and alleviating circadian rhythm disorders in a

mammal. The present invention is further directed to the use of a compound of formula (I) for blocking the phase-shifting effects of light in a mammal.

The present invention further relates to the use of a compound of formula (I) for enhancing or improving sleep quality, in particular by increasing sleep efficiency and augmenting sleep maintenance, as well as for preventing and treating sleep disorders and sleep disturbances, in a mammal.

In a preferred embodiment, the present invention provides a method for the phase advance or phase delay in the circadian rhythm of a subject which comprises administering to the subject an appropriate amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

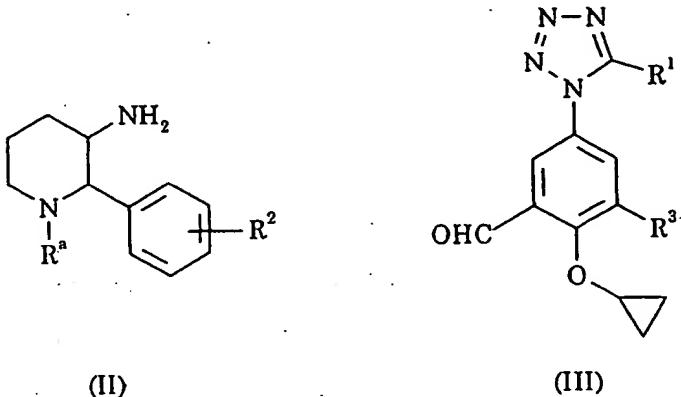
For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and

condition of the patient, and will ultimately be at the discretion of the attendant physician.

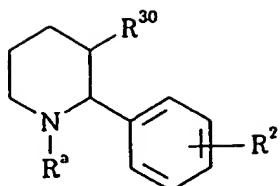
The compounds according to the present invention may be prepared by a process (A) which comprises reacting a compound of formula (II) with 5 a compound of formula (III) in the presence of a reducing agent:



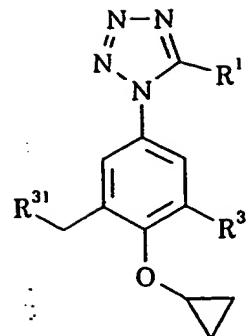
wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined for formula (I), and R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group, followed where necessary by 10 N-deprotection.

Suitable reducing agents for use in this reaction include, for example, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The reaction is conveniently effected in a suitable 15 solvent such as acetic acid, methanol or 1,2-dichloroethane at a temperature between 0°C and 50°C, conveniently at about room temperature.

According to another process (B), the compounds according to the present invention may be prepared by reacting a compound of formula (IV) 20 with a compound of formula (V):



(IV)



(V)

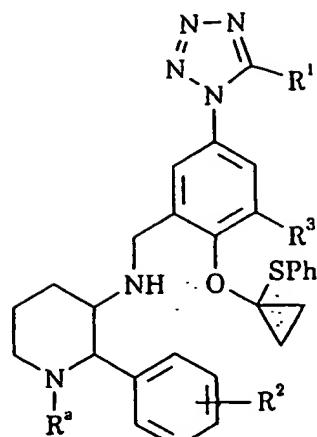
wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined for formula (I), R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group, and one of R<sup>30</sup> and R<sup>31</sup> represents a leaving group and the other of R<sup>30</sup> and R<sup>31</sup> represents NH<sub>2</sub>; in the presence of a base, followed by deprotection, if required.

Suitably R<sup>30</sup> represents NH<sub>2</sub> and R<sup>31</sup> represents a leaving group.

Suitable leaving groups include halogen atoms, e.g. chlorine, bromine or iodine, or sulphonate derivatives such as tosylate, mesylate or triflate.

The reaction is conveniently carried out in a suitable organic solvent, such as an ether, e.g. 1,2-dimethoxyethane, at a temperature in the region of 0°C. Favoured bases of use in the reaction include alkali metal amides and hydrides, such as potassium bis(trimethylsilyl)amide or potassium hydride. Suitably, sodium hydride is used.

According to another general process (C), compounds of formula (I) may be prepared from a compound of formula (VI)

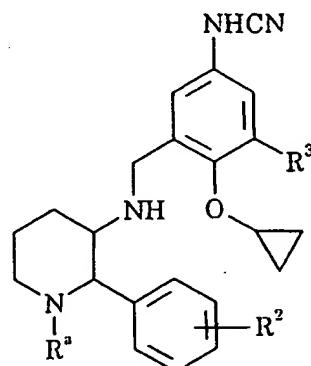


(VI)

wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined for formula (I), R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group, and Ph is a phenyl ring, by reaction with lithium naphthalenide in tetrahydrofuran, followed where necessary by N-deprotection. The reaction is preferably effected at reduced temperature, for example at about -78°C.

According to another general process (D), compounds of formula (I) may be prepared from a compound of formula (VII)

10



(VII)

wherein R<sup>2</sup> and R<sup>3</sup> are as defined for formula (I) and R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group, by reaction with ammonium chloride and sodium azide at elevated temperature, followed where necessary by

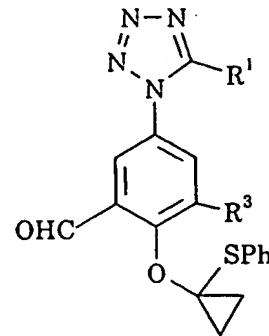
N-deprotection. The reaction is conveniently effected in a solvent such as dimethylformamide.

Further details of suitable procedures will be found in the accompanying Examples.

5      Suitable amino protecting groups include alkoxy carbonyl groups such as *tert*-butoxycarbonyl and trichloroethoxycarbonyl, aralkyloxycarbonyl groups such as benzyloxycarbonyl, or aralkyl groups such as benzyl. Removal of the protecting group is effected by conventional procedures thus, for example, *tert*-butoxycarbonyl groups 10 may be removed under acidic conditions using, for example, trifluoroacetic acid; benzyloxycarbonyl and benzyl groups, may also be removed by hydrogenolysis in the presence of a catalyst, for example, palladium; and trichloroethoxycarbonyl groups may be removed with zinc dust.

15      Methods for the preparation of intermediates of formula (II) and (IV) are well known in the art (see, for instance, European Patent Specification No. 0 436 334-A).

Intermediates of formula (III) may be prepared from a compound of formula (VIII)

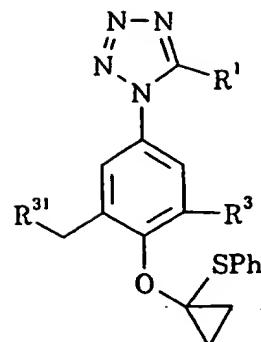


(VIII)

20

using the method of general process (C), above.

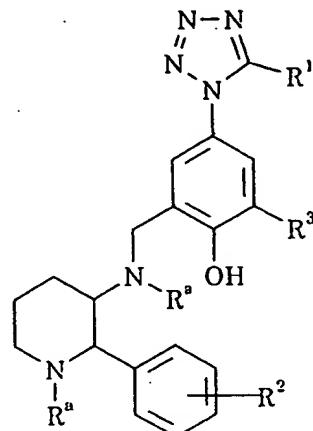
Similarly, intermediates of formula (V) may be prepared from a compound of formula (IX)



(IX)

according to the method of general process (C).

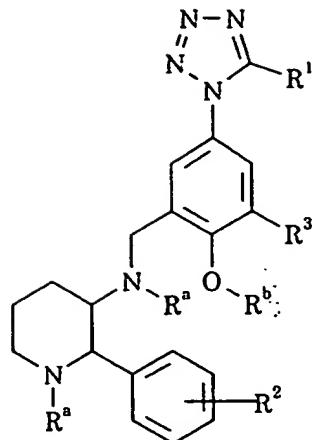
Intermediates of formula (VI) may be prepared from a compound of  
5 formula (X)



(X)

wherein R<sup>1</sup> and R<sup>2</sup> are as defined for formula (I) and R<sup>a</sup> is a hydrogen atom  
10 or a nitrogen protecting group, by reaction with (1-iodo-cycloprop-1-yl)phenylsulphide in the presence of silver carbonate.

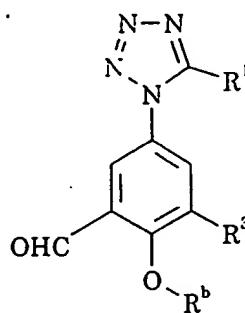
Compounds of formula (X) may be prepared from a compound of  
formula (XI)



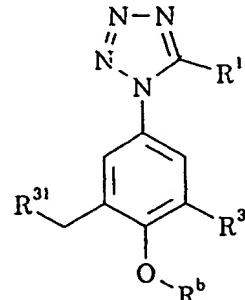
(XI)

where R<sup>b</sup> is a suitable hydroxy protecting group, for example an aralkyl group such as benzyl, by hydrogenation under conventional conditions.

5 Compounds of formula (XI) may be prepared by either of the methods of general process (A) or (B), above, using a suitable protected phenolic precursor of formula (XIIa) or (XIIb)



(XIIa)



(XIIb)

10

in place of the compound of formula (III) or (V), respectively.

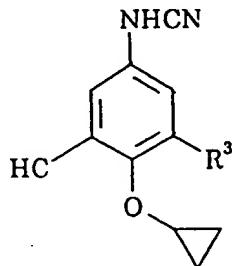
Compounds of formulae (VIII) and (IX) may be prepared by reacting the corresponding phenolic precursors with (1-iodo-cycloprop-1-yl)phenylsulphide in the presence of silver carbonate. The phenolic precursors of compounds of formulae (VIII), (IX), (XIIa) and (XIIb) are

known compounds or may be prepared from known compounds by methods readily apparent to one skilled in the art.

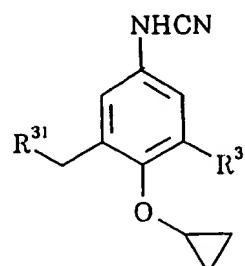
Alternatively, intermediates of formula (III) may be prepared by carbonylation of the corresponding aryl iodide using conventional methodology, for example, by treatment with carbon monoxide in the presence of tetrakis(triphenylphosphine)palladium (0) and tributyl tin hydride.

The aryl iodide precursor may be prepared from the corresponding aniline derivative using, for example, the methodology described herein.

10 Intermediates of formula (VII) may be prepared by either of the methods of general process (A) or (B), above, using a suitable cyanamide precursor of formula (XIIIa) or (XIIIb)



(XIIIa)



(XIIIb)

15

in place of the compound of formula (III) or (IV), respectively.

Compounds of formula (XIIIa) and (XIIIb) may be prepared by reacting the corresponding compounds of formula (III) or (IV) wherein R<sup>1</sup> is hydrogen, or a protected derivative thereof, with n-butyl lithium in a suitable solvent such as tetrahydrofuran.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons,

1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The stereoisomers of the compounds of formula (I) may be separated by procedures known in the art to obtain the preferred (2S,3S) 5 stereoisomers.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC<sub>50</sub> at the NK<sub>1</sub> receptor of less than 1nM on said test method. Thus, for instance, the 10 compounds of Examples 1 and 2 were found to have an IC<sub>50</sub> at the human NK<sub>1</sub> receptor of 0.08nM and 0.13nM, respectively.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

15

### DESCRIPTION 1

#### 5-Nitro-2-(1-phenylthiocycloprop-1-yl)oxybenzenemethanol

Silver carbonate (20g, 72.2mmol) was added to a solution of 2-hydroxy-5-nitrobenzaldehyde (6.5g, 40.1mmol) and (1-iodocycloprop-1-yl)phenylsulfide (Cohen T. and Matz J. R., *J. Am. Chem. Soc.* 1980, 102, 6902) (20g, 72.2mmol) in toluene (60ml) and the mixture was stirred at 40°C for 24 hours. The mixture was cooled, diluted with ethyl acetate and filtered, washing well with ethyl acetate. The mixture was washed with aqueous sodium hydroxide (3 x 100ml) and brine (100ml), dried (MgSO<sub>4</sub>) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethanol (15ml), cooled in ice and sodium borohydride (0.74g, 19.6mmol) was added. The mixture was stirred at room temperature for 1 hour, then water (10ml) was added. The mixture was extracted with ethyl acetate and the combined organic fractions were dried (MgSO<sub>4</sub>) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (95:5

increasing to 50:50), to give the title compound as a yellow solid (5g, 40%).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.48-1.50 (4H, m), 1.80 (1H, t), 4.60-4.62 (2H, d), 7.26-7.45 (6H, m), 8.21-8.29 (1H, dd), and 8.30 (1H, d).

5

### DESCRIPTION 2

#### 5-Amino-2-(1-phenylthiocycloprop-1-yl)oxybenzenemethanol

Iron powder (7.1g, 126.2mmol) was added to a mixture of 5-nitro-2-(1-phenylthiocycloprop-1-yl)oxybenzenemethanol (Description 1; 5g, 15.8mmol) and acetic acid (50ml) in water (150ml) and the mixture was heated to 80°C and stirred overnight. The mixture was cooled and filtered through Celite<sup>TM</sup>, washing the residue thoroughly with ethyl acetate, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with aqueous sodium hydroxide (1M, 3x100ml). The organic layer was dried ( $\text{MgSO}_4$ ) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3(\text{Aq.})$  (96:4:0.4) to give the title compound as an orange oil (2.8g, 62%).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.32-1.50 (4H, m), 3.32 (3H, br s), 4.47 (2H, s), 6.65 (2H, m), 7.13 (1H, d, *J* 8.4 Hz), 7.20-7.34 (3H, m), and 7.46 (2H, m).

### DESCRIPTION 3

#### 5-Amino-2-cyclopropoxybenzenemethanol

Lithium naphthalenide (0.7M solution in THF), was added dropwise to a stirred, cooled (-78°C) solution of 5-amino-2-(1-phenylthiocycloprop-1-yl)oxybenzenemethanol (Description 2; 2.8g, 9.8mmol) in tetrahydrofuran (30ml) until a dark green color persisted. The mixture was stirred at -78°C for 30 minutes, then water (25ml) was added and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate and the combined organic fractions were dried ( $\text{MgSO}_4$ ) and the solvent was evaporated under reduced pressure. The residue was purified

by flash column chromatography on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub>(Aq.) (97:3:0.3) to give the title compound as a yellow solid (1.34g, 77%). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.74-0.75 (4H, d, *J* 4.5 Hz), 2.41-2.50 (1H, br s), 3.42-3.46 (2H, br s), 3.69-3.71 (1H, m), 4.55 (2H, s), 5 6.59 (1H, dd, *J* 8.5, 2.9 Hz), 6.65 (1H, d, *J* 2.9 Hz), and 7.03-7.06 (1H, d, *J* 8.5 Hz).

#### DESCRIPTION 4

##### N-[4-Cyclopropoxy-3-(hydroxymethyl)phenyl]trifluoroacetamide

10 Trifluoroacetic anhydride (3.5ml, 24.7mmol), was added dropwise to a stirred, cooled (-78°C) solution of 5-amino-2-cyclopropoxybenzenemethanol (Description 3; 1.34g, 7.49mmols), and triethylamine, (4.7ml, 33.7mmol) in dichloromethane (20ml), such that the temperature of the mixture did not exceed 15 -65°C. The mixture was stirred at -78°C for 45 minutes, then warmed to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol and the mixture was heated under reflux for 20 minutes. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was 20 dissolved in ethyl acetate, washed with aqueous citric acid (10%, 3x50ml), aqueous sodium hydrogen carbonate (saturated, 3x50ml) and brine (50ml), dried (MgSO<sub>4</sub>), and the solvent was evaporated under reduced pressure to give the title compound as a brown solid (1.74g, 84%). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 0.78-0.84 (4H, m), 2.18 (1H, br s), 3.76-3.81 (1H, m), 4.63 (2H, s), 25 7.26 (1H, d, *J* 8.7 Hz), 7.40-7.41 (1H, d, *J* 2.7 Hz), 7.54-7.57 (1H, dd, *J* 8.7, 2.7 Hz), and 7.87 (1H, br s).

#### DESCRIPTION 5

##### 2-(Cyclopropoxy)-5-(trifluoroacetylamino)phenylmethyl Benzoate

30 Benzoyl chloride (637μL, 5.5mmol) was added to a stirred, cooled (0°C) solution of

N-[4-cyclopropoxy-3-(hydroxymethyl)phenyl]trifluoroacetamide (Description 4; 1.5g, 5.5mmol) and pyridine (884 $\mu$ L, 10.9mmol) in dichloromethane (20ml) and the mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was poured into 5 aqueous sodium hydrogen carbonate (saturated, 75ml) and extracted with ethyl acetate. The combined organic fractions were washed with aqueous sodium hydrogen carbonate (saturated, 3x70ml), aqueous citric acid (10%, 3x70ml) and brine (70ml), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated under reduced pressure. The residue was purified by flash column 10 chromatography on silica gel, eluting with hexane/ethyl acetate (90:10), to give the title compound as a pale yellow solid (1.81g, 88%).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  0.78-0.82 (4H, m), 3.79-3.81 (1H, m), 5.35 (2H, s), 7.28 (1H, d, *J* 8.8 Hz), 7.44-7.48 (3H, m), 7.58 (1H, m), 7.63 (1H, dd, *J* 8.8, 2.7 Hz), 7.77 (1H, br s), and 8.07 (2H, d, *J* 7.6 Hz).

15

#### DESCRIPTION 6

2-(Cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]phenylmethyl Benzoate

Triphenylphosphine (1.88g, 7.16mmol) was added to a suspension of 20 2-(cyclopropoxy)-5-(trifluoroacetylamino)phenylmethyl benzoate (Description 5; 1.81g, 4.78mmol) in carbon tetrachloride (30ml) and the mixture was heated under reflux overnight. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in dimethylformamide (20ml) and added slowly to a suspension 25 of sodium azide (466mg, 7.16mmol) in dimethylformamide (10ml). The mixture was stirred at room temperature for 30 minutes, poured into water (100ml) and extracted with ethyl acetate. The combined organic fractions were washed with water (4x100ml) and brine (100ml), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated under reduced pressure. The 30 residue was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (85:15), to give the title compound as a yellow

oil (1.57g, 81%).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  0.86-0.91 (4H, m), 3.86-3.90 (1H, m), 5.41 (2H, s), 7.44-7.48 (4H, m), 7.54-7.61 (2H, m), and 8.04-8.07 (2H, dd,  $J$  8.4, 1.3 Hz).

5

### DESCRIPTION 7

#### 2-(Cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]benzenemethanol

Aqueous lithium hydroxide (1M, 20ml, 20mmol) was added to a solution of 2-(cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]phenylmethyl benzoate (Description 6; 1.57g, 3.9mmol) in methanol (20ml) and the mixture was stirred at room temperature for 1 hour. The mixture was poured into aqueous sodium hydrogen carbonate (saturated, 100ml) and extracted with ethyl acetate (2x100ml). The combined organic fractions were washed with aqueous sodium hydrogen carbonate (saturated, 3x100ml) and brine (100ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil (1.13g, 97%).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  0.83-0.92 (4H, m), 2.06 (1H, t,  $J$  6.0 Hz), 3.84-3.89 (1H, m), 4.72 (2H, d,  $J$  6.0 Hz), 7.34 (1H, dd,  $J$  8.8, 2.4 Hz), 7.42 (1H, d,  $J$  8.8 Hz), and 7.51 (1H, d,  $J$  2.4 Hz).

20

### DESCRIPTION 8

#### 2-(Cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]benzaldehyde

Sulfur trioxide pyridine complex (2.16g, 13.6mmol) was added to a solution of 2-(cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]benzenemethanol (Description 7; 1.13g, 3.8mmol) and triethylamine, (3.7ml, 26.4mmol) in dimethylsulfoxide and the mixture was stirred at room temperature for 45 minutes. The mixture was poured into aqueous citric acid (10%, 70ml) and extracted with ethyl acetate. The combined organic fractions were washed with aqueous citric acid (10%, 4x70ml), water (3x70ml) and brine (70ml), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was evaporated under reduced pressure to give the title compound as a yellow

solid (0.459g, 41%).  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  0.96-0.98 (4H, m), 3.95-3.99 (1H, m), 7.62 (1H, d,  $J$  8.9 Hz), 7.66 (1H, dd,  $J$  8.9, 2.7 Hz), 7.94 (1H, d,  $J$  2.7 Hz), and 10.42 (1H, s).

5

EXAMPLE 1(2S3S)-N-((2-Cyclopropoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl)methyl)-2-phenylpiperidin-3-amine Dihydrochloride

Sodium triacetoxyborohydride (411mg, 1.94mmol) was added to a mixture of 2-(cyclopropoxy)-5-[5-(trifluoromethyl)tetrazol-1-yl]benzaldehyde (Description 8; 0.459g, 1.54mmol), (2S3S)-2-phenylpiperidin-3-amine (prepared by the method described in WO 95/08549; 0.407g, 2.3mmol) and acetic acid (0.246ml, 4.62mmol) in 1,2-dichloroethane (3ml) and the mixture was stirred at room temperature for 45 minutes. The mixture was poured into aqueous sodium hydrogen carbonate (satd.) and extracted with ethyl acetate. The combined organic fractions were washed with aqueous sodium hydrogen carbonate (satd., 2x70ml) and brine (70ml), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC on silica gel, eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3(\text{Aq.})$  (97:3:0.3). The residue was dissolved in ethanol (3ml) and ethereal hydrogen chloride (1M, 2.5ml) was added. The solvent was evaporated under reduced pressure and the residue was recrystallised from ethanol/water (6:1). The solid was collected and dried *in vacuo* to give the title compound as a colorless solid (0.25g, 30%).  $^1\text{H}$  NMR (360MHz,  $\text{D}_2\text{O}$ )  $\delta$  0.55-0.58 (1H, m), 0.72-0.75 (1H, m), 0.81-0.86 (2H, m), 2.10-2.11 (2H, m), 2.28 (1H, m), 2.47-2.50 (1H, m), 3.29-3.37 (1H, m), 3.69-3.72 (1H, m), 3.76-3.79 (1H, m), 3.96 (1H, m), 4.06 (1H, d,  $J$  13.7 Hz), 4.34 (1H, d,  $J$  13.7 Hz), 4.96 (1H, d,  $J$  3.8 Hz), 7.32 (2H, m), 7.48-7.55 (5H, m), and 7.69-7.72 (1H, dd,  $J$  8.9, 2.6 Hz). m/z (ES $^+$ ) 459 (M+1).

EXAMPLE 2

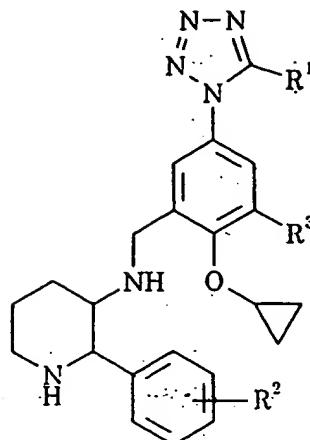
(±)-(2R3R,2S3S)-N-({2-Cyclopropoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl}methyl)-2-(4-fluorophenyl)piperidin-3-amine Dihydrochloride

Prepared from the compound of Description 8 and

5    (±)-(2R3R,2S3S)-2-(4-fluorophenyl)piperidin-3-amine (prepared by the  
method described in WO 95/08549) according to the method of Example 1.  
1H NMR (360MHz, D<sub>2</sub>O) δ 0.59 (1H, m), 0.72-0.75 (1H, m), 0.83-0.86 (2H,  
m), 2.07 (2H, m), 2.25 (1H, m), 2.43 (1H, m), 3.31-3.34 (1H, m), 3.64-3.68  
(1H, m), 3.81-3.82 (1H, m), 3.89 (1H, m), 4.05 (1H, d, *J* 13.7 Hz), 4.31 (1H,  
10    d, *J* 13.7 Hz), 4.94 (1H, d, *J* 3.8 Hz), 7.24-7.28 (2H, m), 7.35-7.39 (2H, m),  
7.50 (1H, d, *J* 2.6 Hz), 7.54 (1H, d, *J* 8.9 Hz), and 7.70 (1H, dd, *J* 8.9, 2.6  
Hz). m/z (ES<sup>+</sup>) 477 (M+1).

CLAIMS:

1. A compound of the formula (I):



5

(I)

wherein

R<sup>1</sup> represents a hydrogen atom or a methyl or trifluoromethyl group;

R<sup>2</sup> represents a hydrogen or halogen atom; and

10 R<sup>3</sup> represents a hydrogen or halogen atom;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein R<sup>1</sup> represents a hydrogen atom or a trifluoromethyl group.

15

3. A compound as claimed in claim 2 wherein R<sup>1</sup> represents a trifluoromethyl group.

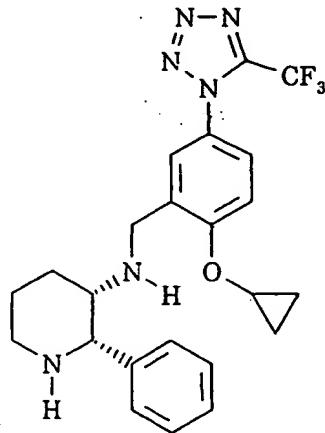
4. A compound as claimed in any one of claims 1 to 3 wherein R<sup>2</sup> 20 represents a hydrogen, fluorine or chlorine atom.

5. A compound as claimed in claim 4 wherein R<sup>2</sup> is a hydrogen atom or a 4-fluorine atom.

6. A compound as claimed in any one of claims 1 to 5 wherein R<sup>3</sup> represents a hydrogen, fluorine or chlorine atom.

5 7. A compound as claimed in claim 6 wherein R<sup>3</sup> is a hydrogen or fluorine atom.

8. A compound as claimed in claim 1 which has the formula (Ia)



10 (Ia)

or a salt thereof.

9. The compound as claimed in claim 8 in the form of a  
15 pharmaceutically acceptable acid addition salt.

10. A compound as claimed in any one of claims 1 to 9 in the form of its (2S,3S) stereoisomer.

20 11. A compound as claimed in claim 1 selected from:

N-{{2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl}methyl}-2-phenylpiperidin-3-amine;

(2*S*,3*S*)-*N*-{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-phenylpiperidin-3-amine;  
*N*-{[2-cyclopropoxy-5-(5-trifluoromethyltetrazol-1-yl)phenyl]methyl}-2-(4-fluorophenyl)piperidin-3-amine;  
5 or a pharmaceutically acceptable salt thereof.

12. A compound as claimed in any preceding claim for use in therapy.

10 13. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 11, together with at least one pharmaceutically acceptable carrier or excipient.

15 14. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1.

20 15. A method according to claim 14 for the treatment or prevention of pain or inflammation, migraine, emesis, posttherapeutic neuralgia, depression or anxiety.

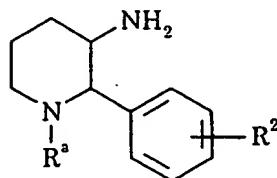
25 16. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

30 17. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of pain or inflammation, migraine, emesis, posttherapeutic neuralgia, depression or anxiety.

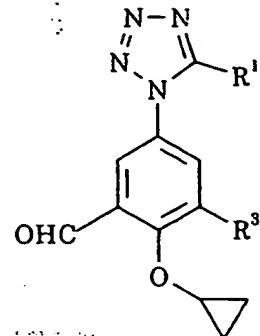
18. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A) reacting a compound of formula (II) with a compound of formula (III) in the presence of a reducing agent:

5



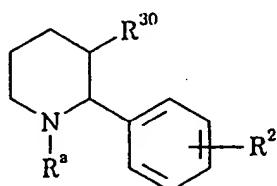
(II)



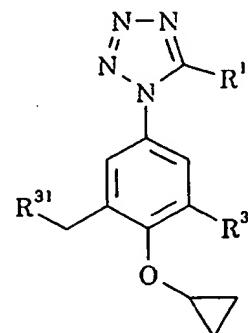
(III)

wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1, and R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group; or

10 (B) reacting a compound of formula (IV) with a compound of formula (V):



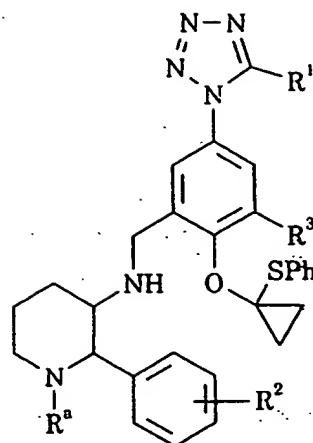
(IV)



(V)

15 wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1, R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group, and one of R<sup>30</sup> and R<sup>31</sup> represents a leaving group and the other of R<sup>30</sup> and R<sup>31</sup> represents NH<sub>2</sub>; in the presence of a base; or

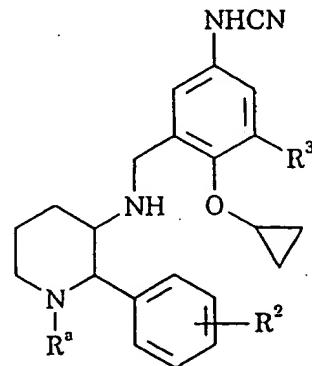
(C) reacting a compound of formula (VI)



(VI)

wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1, R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group, and Ph is a phenyl ring; with lithium naphthalenide in tetrahydrofuran; or

5 (D) reacting a compound of formula (VII)



(VII)

10

wherein R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1, and R<sup>a</sup> is a hydrogen atom or a nitrogen protecting group; with ammonium chloride and sodium azide; each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

and/or, if desired, converting the resulting compound of formula (I) 5 or a salt thereof, into a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/03299

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C07D401/12 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|-----------|--|-----------------------|
| Y         | WO 95 08549 A (GLAXO GROUP LTD ;ARMOUR DUNCAN ROBERT (GB); EVANS BRIAN (GB); GIBL) 30 March 1995<br>cited in the application<br>see claim 1<br>---     | 1-18                  |
| Y         | WO 96 29326 A (GLAXO GROUP LTD ;GIBLIN GERARD MARTIN PAUL (GB); SHARRATT PETER J0) 26 September 1996<br>cited in the application<br>see claim 1<br>--- | 1-18                  |
| X         | WO 96 21661 A (GLAXO GROUP LTD ;ARMOUR DUNCAN ROBERT (GB); GIBLIN GERALD MARTIN P) 18 July 1996<br>cited in the application<br>see claims 1,3<br>---   | 1-18<br>-/-           |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

2 February 1999

Date of mailing of the international search report

10.02.99

Name and mailing address of the ISA

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Authorized officer

Gettins, M

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/03299

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| Y          | WO 97 21702 A (MERCK SHARP & DOHME ;BAKER<br>RAYMOND (GB); ELLIOTT JASON (GB); SWAIN)<br>19 June 1997<br>see claim 1<br>----- | 1-18                  |

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 98/03299

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 14 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/03299

| Patent document cited in search report | Publication date | Patent family member(s) |       | Publication date |
|--|------------------|-------------------------|-------|------------------|
| WO 9508549                             | A 30-03-1995     | AP 495 A                |       | 28-05-1996       |
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|  |                  | AU 7697494 A            |       | 10-04-1995       |
|  |                  | BG 100487 A             |       | 31-12-1996       |
|  |                  | CN 1135218 A            |       | 06-11-1996       |
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|  |                  | DE 69414590 D           |       | 17-12-1998       |
|  |                  | EP 0720609 A            |       | 10-07-1996       |
|  |                  | FI 961270 A             |       | 03-05-1996       |
|  |                  | HR 940575 A             |       | 28-02-1997       |
|  |                  | HU 75648 A              |       | 28-05-1997       |
|  |                  | JP 9505275 T            |       | 27-05-1997       |
|  |                  | NO 961156 A             |       | 21-05-1996       |
|  |                  | NZ 273614 A             |       | 22-09-1997       |
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